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Fungemia in Tertiary Hospitals; An Overview Fungal Profile, Antifungal Resistance, and Antifungal Therapy

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Abstract

Fungemia is a bloodstream infection caused by fungal pathogen and commonly occurs in hospitalized patients with certain risk factors. Indonesia itself is a tropical country with middle income that makes the incidence rate of fungemia tend to be higher, namely10/10,000 people. A recent study about candidemia conducted in Dr. Soetomo General Academic Hospital stated that the most common species that caused candidemia is Candida albicans (33.96%) and the blood sample mostly collected from patients from high care unit and patient with diabetes. We conducted this study to provide a new overview of data on the profile of the causes of fungal infections, patterns of fungal resistance to antifungals, and antifungal therapy in patients with fungemia in hospitalized patients at Dr. Soetomo General Academic Hospital, Surabaya, for the period of January - December 2023. This research is a descriptive study using the patient's medical records. Variables observed in this study include; gender, age, care unit, risk factor, species distribution, resistance pattern, type of antifungal therapy, and duration of antifungal therapy. Mostly the blood cultures are collected from female patients aged 0-9 years old. This study also found that most blood cultures are collected from patients in intensive care unit with use of CVC. Most of the patients did not receive antifungal therapy The most frequent found species is *Candida parapsilosis* with the highest resistance rate found in Amphotericin-B. The most common antifungal that is used is fluconazole which is mostly given within the range of 8-14 days .

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INTRODUCTION

Fungemia is a bloodstream infection caused by fungal pathogen and commonly occurs in hospitalized patients with certain risk factor[1,2]. Fungal pathogen can be divided into two categories; opportunistic and endemic agent which is influenced by geographic factors.[2] Fungemia is one of the problems in intensive care units especially in developing and middle income countries.[1] In Indonesia, the current data of incidence rate of candidemia is 10/10,000 with 30% mortality rate.[3] According to previous study about candidemia in Dr. Soetomo General Academic Hospital, the most common species that caused candidemia is *Candida albicans* (33,96%) and mostly the blood cultures are collected from intensive care units with the most common risk factors being CVC use and patients with diabetes mellitus.[4]

Until now, the gold standard method to diagnose fungemia is blood culture with macroscopic and microscopic examination for antifungal susceptibility test[5] Based on other study, increased number of mortality rate in fungemia patient with high risk factor is caused by fungal resistance; furthermore, it is important to discuss about resistance rate of fungal agents.[6,7]

Research about fungemia has rarely been done in developing countries, especially in Indonesia, although the incidence rate tends to be higher in developing countries. Dr. Soetomo General Academic Hospital itself is a tertiary hospital with many inpatient cases that require intensive care; however, until now there has not been found any study about species distribution of fungemia patients, patterns of fungal resistance, and therapy of fungemia patients. Therefore it is hoped that this study will provide the latest information to improve the management of patients' treatment and reference for study related to fungal bloodstream infection in the future.

MATERIALS AND METHODS

Population and Sample

The data used in this research were secondary data from medical records of inpatients with fungemia in Dr. Soetomo General Academic Hospital from January 2023 until December 2023. The sample used in this research is all medical records that contain patient's demographic data, inpatient unit, risk factor, antifungal sensitivity test results, antifungal therapy and the duration of antifungal therapy use. The total number of fungemia inpatients is 146 and the number of patients that meet all the criteria is 125 patients.

Methods

This research design is an observational study with retrospective approach to observe profile of fungemia inpatients in RSUD Dr. Soetomo within January – December 2023.

RESULTS AND DISCUSSION

The research results showed that the majority of fungemia inpatients is within the children age group between 0 – 9 years old, especially in <0 years old. This finding is similar to previous study about candidemia in Dr. Soetomo General Academic Hospital which stated that the highest incidence rate of candidemia occurred in the age group <0 years old.[4] In patients in the age group age <1 years old the immune system has not fully developed which causes them to be more susceptible to fungal pathogen.[6] A common immunological that effectively kills fungal pathogen is Th1 or Th17 immune response which only develops at early childhood stage > 1 year old.[8] As

shown in Table 1, there are not significant differences between number of male and female fungemia inpatients, which is relevant to previous study that stated gender is not the main risk factor in fungemia.[4,1] The majority of the blood cultures are isolated from the patients in ICU followed by patients in HCU. This study has similar results to other study that fungemia is more common among ICU patients due to many invasive procedures that tend to be occurred in ICU.[9,10] Fungemia tends to be an opportunistic infection which mainly infects individuals with risk factors.[11] In this study, most of the patients had several risk factors. Table 1 shows that in this research the most common risk factor is CVC usage. This result is similar to previous study that CVC usage is a common risk factor in fungemia patients due to catheters used are contaminated with fungal pathogens.[4,12]

Table 1. Characteristics of fungemia inpatients in Dr. Soetomo Surabaya General Academic Hospital, January 2023 – December 2023

Predictor	Amount	Percentage
Age		
0 – 9 years old	66	52.80
10 – 19 years old	9	7.20
20 – 29 years old	3	2.40
30 – 39 years old	9	7.20
40 – 49 years old	9	7.20
50 – 59 years old	15	12.00
>59 years old	14	11.20
Gender		
Male	62	49.60
Female	63	50.40
Medical Units		
Intensive care unit	33	26.40
High care unit	30	24.00
Pediatric wards	15	12.00
Medical wards	13	10.40
Neonatal intensive care unit	13	10.40
Surgery wards	9	7.20
Neonatal high care unit	6	4.80
Isolation wards	4	3.20
Pediatric intensive care unit	1	0.80
Pediatric high care unit	1	0.80

Risk Factor	Frequency n(%), n=125
CVC	44.00%
TPN	40.00%
Surgery	38.40%
Use of broad spectrum antibiotics > 14 days	24.80%
Preterm infants	21.60%
Patient with diabetes mellitus	13.60%
CKD	9.60%
Malignancy	7.20%
Immunocompromised	4.80%

Based on Table 2, the blood culture results from fungemia inpatient in 2023 found 125 fungal isolates with 15 species. The species that is commonly found in the blood culture is *Candida parapsilosis* (40.0%) followed by *Candida tropicalis* (20.00%) and *Candida glabarata* (12.00%). The results about species distribution on this study is not common, because several other studies had the result that the common cause of fungemia is *Candida albicans* which is believed to be caused by the azole antifungal used was not very common at that time.[13,4] However, currently, use of azole antifungals as therapy is very common which leads to decreased incidence of *Candida albicans* fungemia.[14] However this has caused an increasing incident of Candida non-albicans caused by Candida non-albicans resistance to azole antifungals.[14] A study having a similar result to this study was conducted in Japan that showed *Candida parapsilosis* being the most common species found in fungemia patients.[15] This is believed caused by use of echinocandins as antifungal treatment which is not relevant with this study because only two patients received echinocandin as antifungal theraphy.[15]

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Improper use of antifungal treatment could lead to fungal resistance which has many predisposing factors that can lead to antifungal resistance.[16] Antifungal resistance mechanism in Candida species includes gene mutation, efflux pump overexpression, and biofilm formation.[17] Another study stated the incidence rates of fungemia caused by *Candida parapsilosis* have increased over the last two decades due to nosocomial transmission from prolonged use of medical devices such as Central Venous Catheter (CVC) and Top Parenteral Nutrition (TPN).[1418] Another study stated that *Candida parapsilosis* has ability to form biofilm on Central Venous Catheter or other prosthetic material and ability to grow in Top Parenteral Nutrition solutions, by which it can be concluded that *Candida parapsilosis* blood stream infections (BSI) are related to the exogenous route of fungal infection, which is relevant to this study.[19] In this study, *Candida tropicalis* is the most common fungal pathogen found in the patient's blood culture after *Candida parapsilosis*. Several studies conducted in tropical countries concluded that fungemia caused by *Candida tropicalis* commonly occurred in tropical countries such as Latin America and Asia.[20,21] Several studies stated that the decreased incidence of fungemia caused by *Candida albicans* is believed due to increased use of azole antifungals each year while the resistance rate of azole in *Candida albicans* species tends to be lower, which causes the change of incidence rate between fungemia caused by *Candida albicans* and *Candida non-albicans* each year.[22,4]

Table 2. Fungal species distribution from fungemia inpatients in Dr. Soetomo Surabaya General Hospital, January 2023 – December 2023

Species	Frequency	Percentage
Candida non-albicans		
Candida parapsilosis	51	40.80%
Candida tropicalis	26	20.80%
Candida glabarata	15	12.00%
Candida haemulonii var vulnera	5	4.00%
Candida haemulonii	4	3.20%
Candida duobushaemulonii	3	2.40%
Candida dubliniensis	1	0.80%
Candida guilliermondii	1	0.80%
Candida krusei	1	0.80%
Candida lusitaniae	1	0.80%
Candida rugosa	1	0.80%
Candida utilis	1	0.80%
Candida albicans	11	8.80%
Cryptococcus neoformans	2	1.60%
Kodamaea ohmeri	2	1.60%

Antifungal that is used for therapy is one of the main factors for successful therapy in fungemia patients; therefore, the patients that show symptoms of fungemia have to do a blood culture test to check whether there is an fungal pathogen and its sensitivity pattern.[1] As shown in Table 3, there are found several isolates that are resistant to Amphotericin-B, Micafungin, and Caspofungin which tends to be different from other study. Other study stated that fungal pathogens are commonly susceptible to echinocandin and polyene.[23] However, there is a study that has similar results by which Amphotericin-B has a high resistance rate especially in *Candida non-albicans* isolate.[24] Fungal resistance to Amphotericin-B is associated with ERG-3 gene mutation while fungal resistance to Micafungin and Caspofungin is linked to mutation in units FKS1 and FKS2.[2526] Furthermore, in this study there are found several isolates from *Candida non-albicans* that are resistant to azole antifungals such as Fluconazole and Voriconazole. Several studies stated that resistance to azole antifungals are commonly occurred in *Candida non-*

albicans isolate especially in *Candida glabarata* which is linked with mutation in ERG-11 gene.[27,23,28] Therefore, in this research it can be concluded that the most frequent found species is *Candida parapsilosis* with highest resistance rate found in Amphotericin-B. In several studies it is stated that there is found a significant degree of resistance rate of Amphotericin-B in *Candida parapsilosis* isolates.[29]

Table 3. Resistance rate to antifungal of fungemia inpatients in Dr. Soetomo Surabaya General Hospital, January 2023 – December 2023

Species (Frequency)	Antifungal (Isolates)	Resistance (%)
Candida albicans **(11)**	Amphotericin-B (11)	9.09
	Micafungin (11)	9.09
Candida non-albicans **(110)**	Fluconazole (88)	1.14
	Voriconazole (102)	1.96
	Caspofungin (83)	4.82
	Amphotericin-B (105)	11.3
	Flucytosin (107)	0.93
	Micafungin (93)	1.08

As shown in Table 4, 52% patients having fungal pathogen from the blood culture test were not treated with antifungal treatment, which is relevant to the Infectious Disease Society of America (IDSA) guideline that stated antifungal treatment should be given to patients tested positive for fungal pathogen in blood culture and having symptoms of infections such as fever.[30] This study further shows that the outcomes of the patient given antifungal treatment is that 56% of the patients are discharged. However, a successful therapy involves many other factors such as risk factors and duration of the treatment.[9] Based on Table 5, most of the patients that met the criteria to receive antifungal treatment were given fluconazole, which is similar to a study conducted in Tehran.[13] It occurs because Fluconazole is a broadspectrum antifungal and has several mechanisms of action such as overexpression of ERG-11 gene which is caused by the existence of Upc2 transcription factor and mutation of ERG-3 gene which cause thinning of the ergosterol wall.[31,28] In this study, it was also found that antifungal treatment is mostly given within the range of 8-14 days; however, several patients were discharges and there was not found a continuation of antifungal treatment.

Table 4. Antifungal therapy of fungemia inpatients in Dr. Soetomo Surabaya General Academic Hospital, January 2023 – December 2023

	Frequency	Percentage
Treated with antifungal	60	48%
Not treated with antifungal	65	52%

Table 5. Antifungal therapy and duration of antifungal therapy given to fungemia inpatients in Dr. Soetomo Surabaya General Academic Hospital, January 2023 – December 2023

	Frequency (%) n=60
Antifungal	
Fluconazole	58 (96.67%)
Micafungin	2 (3.33%)
Duration	
1-7 days	58 (96.67%)
8-14 days	2 (3.33%)
15-21 days	58 (96.67%)
22-28 days	2 (3.33%)
29-35 days	58 (96.67%)

STRENGTH AND LIMITATION

The strength of this study is there are not many studies about fungemia, especially in Indonesia, even though the incidence rates are high among ICU patients.

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However, the limitations of this study were due to incomplete medical records especially on the duration of antifungal treatment, which caused inadequate data of duration of antifungal therapy.

CONCLUSIONS

This study shed light on the species distribution, patterns of antifungal resistance, and therapy of fungemia patients in Dr. Soetomo General Academic Hospital, Indonesia. The most frequent found species is *Candida parapsilosis* with highest resistance rate found in Amphotericin-B. Most of the patients did not receive antifungal therapy. Early detection and proper treatment is important for successful treatment of fungemia patients. This study highlights the importance of giving proper treatment to increase successful rate of treatment and decrease the risk of antifungal resistance of fungemia patients.

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ETHICAL CLEARANCE

The use of medical records for the data in this research is approved by the ethics committee of Dr. Soetomo Surabaya General Academic Hospital (1691/LOE/301.4.2/VI/2024).

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CONFLICT OF INTEREST

All of the authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Every author in this study equally contributed from the design to the implementation of the research, result analysis, and writing the manuscript.

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